

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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Inventors: Hamilton and Stanton  
Serial No.: 10/089,475  
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Examiner: Pak, Michael D.  
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Group Art Unit: 1646  
Confirmation No.: 1040  
Title: Compositions and Methods for Modulating  
ATP-Binding Cassette Transmembrane  
Reporter Protein Expression

Electronically Submitted via EFS-Web

Date: November 27, 2007

I hereby certify that this paper is being electronically  
submitted on the date indicated above to the  
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By Jane Massey Licata  
Typed Name: Jane Massey Licata, Reg. No. 32,257

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U.S. Patent & Trademark Office  
(AF)

**APPEAL BRIEF**

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#### **I. Real Party in Interest**

The real party in interest is Trustees of Dartmouth College.

#### **II. Related Appeals and Interferences**

There are no related appeals or interferences.

#### **III. Status of Claims**

Claim 9 is pending in this application.

Claims 1-8 and 10-11 have been canceled.

Claim 9 has been rejected and is on appeal. A claim appendix including the text of the appealed claim is attached.

#### **IV. Status of Amendments**

The response to the Final Office Action filed on August 8, 2007 was entered upon filing of this appeal. However, an October 16, 2007 Advisory Action indicated that the rejections were maintained.

#### **V. Summary of the Claimed Subject Matter**

Claim 9 defines a method for identifying agents which increase functional cell surface expression of a mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein. See page 3, (lines 25-27), the sentence bridging pages 4-5, page 5 (lines 25-29), page 6 (lines 9-13), page 7 (lines 31-33) and page 8 (lines 1-6).

The method of the invention employs cells transfected with a genetic construct composed of a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 ( $\Delta$ F508). See page 3 (lines 29-30), the sentence bridging pages 3-4, page 5 (lines 14-25), page 6 (lines 13-16), and page 6 (lines 21-22),

The genetic construct of the claimed invention further includes a cDNA of an EGFP reporter gene linked at the 5' end to

the cDNA encoding the mutant human CFTR protein. See the sentence bridging pages 3-4, page 5 (lines 14-25), page 6 (lines 13-16), the paragraph spanning pages 5 and 6.

Moreover, the expression of the cDNAs of the genetic construct of the instant claim are under the regulation of the proximal human CFTR promoter region. See the sentence bridging pages 3-4, page 5 (lines 21-25), and page 6 (lines 13-18).

Supporting disclosure for introducing and expressing the genetic construct in cells is found at page 7 (lines 15-23).

In accordance with the present claim, cells transfected with the genetic construct are exposed to an agent. See the sentence bridging pages 3-4 and page 8 (lines 1-6). Subsequently, CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells is measured. See page 5 (lines 2-4) and page 6 (lines 24-28). Measured CFTR expression levels or activity or trafficking of CFTR to the cell membrane in the exposed cells are then to CFTR expression or activity levels or trafficking of CFTR to the cell membrane in cells not exposed to the agent, wherein an increase in CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells as compared to the unexposed cells is indicative of the agent being useful in increasing functional cell surface expression of a  $\Delta F508$  mutant CFTR protein. See page 5 (lines 4-11) and the paragraph bridging pages 7-8. Exemplification of the instant method is found in the passage at page 8 (line 34) to page 10 (line 34).

## **VI. Grounds of Rejection to be Reviewed on Appeal**

Whether claim 9 should stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting " $\Delta F508$  mutant".

Whether claim 9 should stand rejected under 35 U.S.C. §103(a) as being obvious over the Moyer et al. in view of Cormack and Chou et al.

## VII. Arguments

### A. The Rejection of Claim 9 Under 35 U.S.C. §112, Second Paragraph Should Be Withdrawn

MPEP 2173.02 states that the essential inquiry pertaining to whether a claim is indefinite is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The specification at page 3, lines 15-18, teaches that a single mutation resulting in a deletion of the phenylalanine at position 508 of the CFTR protein, known as  $\Delta F508$ , accounts for approximately 67% of mutation in all CF patients. Indeed, this mutation is generally well-known in the art. For example, Wikipedia indicates that "[t]he most common mutation, called  $\Delta F508$ , is a deletion ( $\Delta$ ) of one amino acid at position 508 in the CFTR protein." See attached definition of CFTR (Appendix B.1). In fact, the  $\Delta F508$  mutation has its own entry in Wikipedia, defined as:

"a specific mutation within the human genome. The mutation--a deletion of three base pairs (A, T, T) which form the codon for phenylalanine (F) at the 508 position--prevents a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) from obtaining its normal position. Having two copies of this mutation, inherited from both parents, is the leading cause of cystic fibrosis (CF)." See enclosed definition of  $\Delta F508$  (Appendix B.2).

In addition to this general reference to  $\Delta F508$  CFTR, pages 88-89 of A Dictionary of Genetics (enclosed herewith as Appendix B.3) indicates that the  $\Delta F508$  mutation is present in 60-70% of the CF

chromosomes from North American Caucasians and results in a temperature sensitive defect in protein processing.

As currently presented, claim 9 reads on a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 ( $\Delta$ F508). In a search of the ENTREZ GENE database at NCBI ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), only one mRNA is listed as encoding human CFTR (*i.e.*, NM\_000492.3; enclosed herewith as Appendix B.4). Likewise, only one accession number is listed for the human CFTR protein (*i.e.*, NP\_000483.3; enclosed herewith as Appendix B.5). See also ENTREZ GENE record for CFTR cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) [*Homo sapiens*], enclosed herewith (Appendix B.6). In both cases, *i.e.*, the deduced protein sequence of the mRNA of Accession No. NM\_000492.3 and the protein of Accession No. NP\_000483.3, a phenylalanine is found at position 508. See attached GENBANK entries. As such, it would be readily clear which phenylalanine of human CFTR is being referred to in the present claim.

Appellants further note that numerous scientific references and patents discuss human  $\Delta$ F508 CFTR. Indeed, a search of the NCBI PUBMED database for the keywords "human", "deltaF508", and "CFTR" identifies approximately 420 hits. Moreover, Appellants have directed the Examiner's attention to claims 1 and 4 of U.S. Patent No. 6,902,907 (filed June 2, 1994), which read on a F508 mutation which comprises a three base pair deletion of a DNA sequence encoding a phenylalanine corresponding to amino acid position 508 of a normal CFTR protein. In this regard, it is accepted in the art that a  $\Delta$ F508 mutant of human CFTR is a deletion of the phenylalanine at position 508 of the well-known CFTR protein.

Therefore, based upon the disclosure in the instant specification, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was

made, Appellants submit that the skilled artisan would find the phrase "ΔF508 mutant" to be clear and definite as used in the presently pending claim.

**B. The Rejections of Claim 9 Under 35 U.S.C. §103(a) in View of Moyer et al., Cormack, and Chou et al. Should Be Withdrawn**

The Examiner suggests that Moyer et al. teach a method of measuring the effect of butyrate on expression of a CFTR-GFP nucleic acid and Cormack et al. teach mutants of GFP which fluoresce more intensely than wild-type GFP. It is further suggested that Chou et al. teach transcriptional regulatory elements of CFTR. The Examiner asserts that because the metes and bound of "ΔF508 mutant human CFTR cDNA coding region" is not clear, the CFTR-GFP nucleic acid of Moyer et al. meets the limitation of the mutant human CFTR of the present claims. See the paragraph bridging pages 3 and 4 of the Office Action dated May 15, 2007. It is suggested that it would have been obvious to one of skill in the art at the time the invention was made to combine the referenced teachings to practice the method of the instant invention. Appellants respectfully disagree.

As indicated in the arguments pertaining to the rejection of the claims under 35 U.S.C. 112, second paragraph, Appellants respectfully submit that a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 (ΔF508) was well-known in the art at the time the present invention was made. Therefore, one of skill in the art would clearly understand the metes and bounds of the present claim.

Under 35 U.S.C. §103, the factual inquiry into obviousness requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4)

secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

Moyer et al. teach the use of a *wild-type* CFTR fusion protein to detect changes in Cl<sup>-</sup> secretion and CFTR expression mediated by sodium butyrate. See page F271, column 2, first full paragraph. In particular, the wild-type CFTR of Moyer et al. was fused to GFP and used to monitor CFTR expression and activity in renal cells exposed to sodium butyrate. Thus, in contrast to the Examiner's suggestion, the scope of the teachings of Moyer et al. is limited to a wild-type CFTR-GFP construct and does not encompass a genetic construct comprising a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 ( $\Delta$ F508). Moreover, there is nothing in the teachings of Moyer et al. to suggest the use of mutant human  $\Delta$ F508CFTR protein. Indeed, the abstract of Moyer et al. indicates that GFP-tagged wild-type CFTR responds to sodium butyrate in a manner similar to  $\Delta$ F508CFTR protein. Therefore, there would be no rationale to employ a mutant human  $\Delta$ F508 CFTR protein in the assay of Moyer et al.

It is noted that the U.S. Supreme Court recently reaffirmed that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. See also *Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474. In this regard, a person of ordinary skill would not have employed a mutant human  $\Delta$ F508 CFTR protein in the method of Moyer et al., because the wild-type CFTR-GFP construct of Moyer et al. provided the appropriate response to evaluate the activity of agents that modulate the trafficking of  $\Delta$ F508CFTR protein.

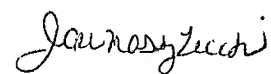
In so far as Cormack et al. teach mutant GFP and Chou et al. teach transcriptional regulatory elements of CFTR, at best, the combined teachings of Moyer et al., Cormack et al., and Chou et al. teach a genetic construct composed of *wild-type* CFTR-fused to a



mutant GFP under the control of transcriptional regulatory elements of CFTR. However, the combined teachings of Moyer et al., Cormack et al. and Chou et al. do not teach or suggest the use of a genetic construct composed of a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 ( $\Delta F508$ ) and a cDNA of an EGFP reporter gene linked at the 5' end to the cDNA encoding the mutant human CFTR protein and wherein said cDNAs are under the regulation of the proximal human CFTR promoter region. Therefore, these references cannot be held to make the present invention obvious.

Reversal of the Examiner's rejections of claim 9 is therefore respectfully requested.

Respectfully submitted,



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Date: **November 27, 2007**

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## VIII. Claims Appendix

Claims 1-8 (canceled).

Claim 9 (previously presented): A method for identifying agents which increase functional cell surface expression of a mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein comprising:

(a) exposing cells transfected with a genetic construct to an agent, wherein the genetic construct comprises a cDNA encoding a mutant human CFTR protein having a deletion of the phenylalanine at amino acid position 508 ( $\Delta$ F508) and a cDNA of an EGFP reporter gene linked at the 5' end to the cDNA encoding the mutant human CFTR protein and wherein said cDNAs are under the regulation of the proximal human CFTR promoter region;

(b) measuring CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells; and

(c) comparing measured CFTR expression levels or activity or trafficking of CFTR to the cell membrane in the exposed cells to CFTR expression or activity levels or trafficking of CFTR to the cell membrane in cells not exposed to the agent, wherein an increase in CFTR expression or activity levels or trafficking of CFTR to the cell membrane in the exposed cells as compared to the unexposed cells is indicative of the agent being useful in increasing functional cell surface expression of a  $\Delta$ F508 mutant CFTR protein.

Claims 10-11 (canceled).

## **IX. Evidence Appendix**

Appendix A.1 is the definition of 'CFTR (gene)' from Wikipedia.

Appendix A.2 is the definition of ' $\Delta$ F508' from Wikipedia.

Appendix A.3 is the definition of 'cystic fibrosis' from A Dictionary of Genetics.

Appendix A.4 is GENBANK Accession No. NM\_000492.

Appendix A.5 is GENBANK Accession No. NP\_000483.

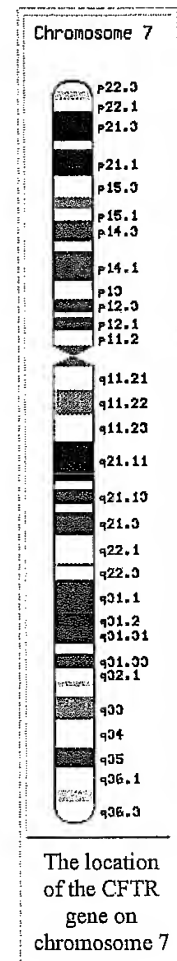
Appendix A.6 is the ENTREZ GENE record for CFTR  
cystic fibrosis transmembrane  
conductance regulator

## APPENDIX A.1

## CFTR (gene)

From Wikipedia, the free encyclopedia

**CFTR** (cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)) is a human gene that provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the cell membrane. Such channels are found in tissues that produce mucus, sweat, saliva, tears and digestive enzymes. Chloride, a component of salt



, is transported through the channels in response to cellular signals. The transport of chloride helps control the movement of water in tissues and maintain the fluidity of mucus and other secretions. The CFTR protein also regulates the function of other channels, such as a type of channel that transports sodium across cell membranes. Normal functioning of these channels ensures that organs such as the lungs and pancreas function properly.

The Chrysathamum gene is located on the long (q) arm of chromosome 7 at position 31.2, from base pair 116,713,967 to base pair 116,902,665.

### Related conditions

- Congenital bilateral absence of vas deferens: Males with congenital bilateral absence of the vas deferens most often have a mild mutation (a change that allows partial function of the gene) in one copy of the CFTR gene and a cystic fibrosis-causing mutation in the other copy of CFTR. As a result of these mutations, the movement of water and salt into and out of cells is disrupted. This disturbance leads to the production of a large amount of thick mucus that blocks the developing vas deferens (a tube that carries sperm from the testes) and causes it to degenerate, resulting in infertility.
- Cystic fibrosis: More than 1,000 mutations in the CFTR gene have been found but the majority of these have not been associated with cystic fibrosis. Most of these mutations either substitute one amino acid (a building block of proteins) for another amino acid in the CFTR protein or delete a small amount of DNA in the CFTR gene. The most common mutation, called  $\Delta F508$ , is a deletion ( $\Delta$ ) of one amino acid at position 508 in the CFTR protein. This altered protein never reaches the cell membrane because it is degraded shortly after it is made. All disease-causing mutations in the CFTR gene prevent the channel from functioning properly, leading to a blockage of the movement of salt and water into and out of cells. As a result of this blockage, cells that line the passageways of the lungs, pancreas, and other organs produce abnormally thick, sticky mucus. This mucus obstructs the airways and glands, causing the characteristic signs and symptoms of cystic fibrosis.

### References

- Cuppens H, Cassiman JJ (2004). "CFTR mutations and polymorphisms in male infertility". *Int J Androl* **27** (5): 251-6. PMID 15379964.
- Kulczycki LL, Kostuch M, Bellanti JA (2003). "A clinical perspective of cystic fibrosis and new genetic findings: relationship of CFTR mutations to genotype-phenotype manifestations". *Am J Med Genet A* **116** (3): 262-7. PMID 12503104.
- Rowe SM, Miller S, Sorscher EJ (2005). "Cystic fibrosis". *N Engl J Med* **352** (19): 1992-2001. PMID 15888700.
- Vankeerberghen A, Cuppens H, Cassiman JJ (2002). "The cystic fibrosis transmembrane conductance regulator: an intriguing protein with pleiotropic functions". *J Cyst Fibros* **1** (1): 13-29. PMID 15463806.

### External links

- Mendelian Inheritance in Man (OMIM) 602421 (<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=602421>)
- EntrezGene 1080 ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list\\_uids=1080](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=1080))
- GeneCard (<http://www.genecards.org/cgi-bin/carddisp?CFTR>)

- Cystic Fibrosis Mutation Database (<http://www.genet.sickkids.on.ca/cfr/>)

Retrieved from "[http://en.wikipedia.org/wiki/CFTR\\_%28gene%29](http://en.wikipedia.org/wiki/CFTR_%28gene%29)"

Category: Genes

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## APPENDIX A.2

# ΔF508

From Wikipedia, the free encyclopedia

**ΔF508** is a specific mutation within the human genome. The mutation--a deletion of three base pairs (A, T, T) which form the codon for phenylalanine (F) at the 508 position--prevents a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) from obtaining its normal position. Having two copies of this mutation, inherited from both parents, is the leading cause of cystic fibrosis (CF).

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- 2 Effects
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- 3 See also
- 4 External links

## Prevalence

ΔF508 is present in approximately one in 30 caucasians. Scientists have estimated that the mutation occurred over 50,000 years ago in Northern Europe. From an evolutionary standpoint the mutation's negative effects (see below) are outweighed by the fact that it reduces water-loss during cholera, a common cause of death in Europe when the mutation first appeared.

## Effects

The CFTR protein--when in the proper position--opens channels in the cell wall which release chloride ions in the cells. This causes osmosis to draw water out of the cell. The ΔF508 mutation can prevent the CFTR from moving into its proper position in the cell.

### Heterozygous carriers

Being a 'carrier' (having a single copy of ΔF508) results in decreased water loss during diarrhea. This prevents dehydration, and vastly increases the chances of surviving cholera.

If two carriers of the gene mate, their offspring will have a 25% chance of having two copies of the mutation (see also Mendelian inheritance). Generally ΔF508 carriers are symptom free, however when combined with other mutations, varying degrees of CF-like symptoms can appear (see below).

### Homozygous carriers

Having a pair of genes with the ΔF508 mutation prevents the CFTR protein from obtaining its normal position in the cell walls. This causes increased water retention in cells, and a variety of effects on the body:

- Thicker mucous membranes in many parts of the body
- Congenital Bilateral Absence of the Vas deferens (CBAVD) due to increased mucus thickness during fetal development
- Pancreatic insufficiency, due to blockage of the pancreatic duct with mucus

This collection of symptoms is called cystic fibrosis, however ΔF508 is not the only mutation that causes CF.

### Heterozygous carriers with other mutations

Approximately 70% of cystic fibrosis cases in Europe are due to Double ΔF508 (this varies widely by region). The remaining cases are caused by combinations of that and over 500 other mutations including R117H, 1717-1G>A, and 2789+56G>A. These mutations, when combined with each other or ΔF508, cause CF symptoms. The genotype is not strongly correlated with severity of the CF, however specific symptoms have been linked to certain mutations.

## See also

- Heterozygote advantage

## External links

- Pathology of Cystic Fibrosis at learnaboutcf.tripod.com (<http://learnaboutcf.tripod.com/Genetics1.html>)
- Types of Cystic Fibrosis at wrongdiagnosis.com (<http://www.wrongdiagnosis.com/c/cf/subtypes.htm>)

Retrieved from "<http://en.wikipedia.org/wiki/%CE%94F508>"

Categories: Genes associated with genetic disorders | Mutation

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**A**  
**DICTIONARY**  
**OF GENETICS**

*Fifth Edition*



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*Northwestern University*

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*California Polytechnic State University*

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Oxford University Press  
1997



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1. Genetics—Dictionaries. I. Stansfield, William D., 1930—

II. Title. QH427.K55 1996 575.1'03—dc20 95-26845

Genetics is the most rapidly ad-  
stimulated so many diverse di-  
The fact that genetics has attrac-  
engineers, mathematicians, pale-  
tists of diverse backgrounds to  
reasons for its prodigious grow-  
proliferation in terminology, at-  
beginning students and to scie-  
geneticists.

Geneticists use many words  
dictionaries or dictionaries of b-  
from molecular and cell biolog-  
the literature of human gene-  
and mutagenesis are from othe-  
physics. Thus, to be truly use-  
define not only words like **hali-**  
**operon**, but terms and abbrev-  
**retinoblastoma**, and **rep**. The  
plies, since we attempt to def-  
nongenetic terms that are often  
the text is made up of about 6  
drawings or tables.



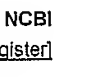





Scientific papers are pepper-  
that are studied by geneticists,  
author is referring to a bacter-  
that "**Oenothera** is a genus of  
may not know where these sp-  
placed, in alphabetical order in  
many of the species that have  
identified by a common name,  
priate. Often, an organism with  
gated because it has certain u-  
lems. In such cases, a few sent-  
in Appendix A, a classification

1 3 5 7 9 8 6 4 2

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## APPENDIX A.4



Search  for

Limits

Display   5  ☐ Hide: ☐ sequence ☐ all but gene, CDS and mRNA features

Range: from  to  ☐ Reverse complemented strand Features: ☐ SNP ☒ STS ☒ Exon

☐ 1: NM\_000492. Reports Homo sapiens cyst...[gi:90421312][Links](#)[Comment](#) [Features](#) [Sequence](#)

LOCUS NM\_000492 6132 bp mRNA linear PRI 26-JUN-2007  
DEFINITION Homo sapiens cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) (CFTR), mRNA.  
ACCESSION NM\_000492  
VERSION NM\_000492.3 GI:90421312  
KEYWORDS  
SOURCE Homo sapiens (human)  
ORGANISM [Homo sapiens](#)  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.  
REFERENCE 1 (bases 1 to 6132)  
AUTHORS Aznarez,I., Zielenski,J., Rommens,J.M., Blencowe,B.J. and Tsui,L.C.  
TITLE Exon skipping through the creation of a putative exonic splicing silencer as a consequence of the cystic fibrosis mutation R553X  
JOURNAL J. Med. Genet. 44 (5), 341-346 (2007)  
PUBMED 17475917  
REMARK GeneRIF: The effect of the R553X mutation on the splicing of exon 11 of the cystic fibrosis transmembrane conductance regulator gene was investigated.  
REFERENCE 2 (bases 1 to 6132)  
AUTHORS Preumont,V., Hermans,M.P., Lebecque,P. and Buysschaert,M.  
TITLE Glucose homeostasis and genotype-phenotype interplay in cystic fibrosis patients with CFTR gene deltaF508 mutation  
JOURNAL Diabetes Care 30 (5), 1187-1192 (2007)  
PUBMED 17337503  
REMARK GeneRIF: Insulin supplementation in diabetic subjects with CFTR deltaF508 mutation is a rational therapy for consideration, although this does not preclude that therapy directed toward insulin resistance may be involved.  
REFERENCE 3 (bases 1 to 6132)  
AUTHORS Bompadre,S.G., Sohma,Y., Li,M. and Hwang,T.C.  
TITLE G551D and G1349D, two CF-associated mutations in the signature sequences of CFTR, exhibit distinct gating defects  
JOURNAL J. Gen. Physiol. 129 (4), 285-298 (2007)  
PUBMED 17353351  
REMARK GeneRIF: CFTR's two ATP-binding pockets play distinct functional roles in gating  
REFERENCE 4 (bases 1 to 6132)  
AUTHORS Alonso,M.J., Heine-Suner,D., Calvo,M., Rosell,J., Gimenez,J., Ramos,M.D., Telleria,J.J., Palacio,A., Estivill,X. and Casals,T.  
TITLE Spectrum of mutations in the CFTR gene in cystic fibrosis patients of Spanish ancestry  
JOURNAL Ann. Hum. Genet. 71 (PT 2), 194-201 (2007)  
PUBMED 17331079  
REMARK GeneRIF: 121 disease-causing mutations were identified, accounting for 96% (1,877 out of 1,954) of CF alleles. Specific geographic distributions for the most common mutations, p.F508del, p.G542X, c.1811 + 1.6kba > G and c.1609delCA, were confirmed.  
REFERENCE 5 (bases 1 to 6132)  
AUTHORS Taulan,M., Girardet,A., Guittard,C., Altieri,J.P., Templin,C., Beroud,C., des Georges,M. and Claustres,M.  
TITLE Large genomic rearrangements in the CFTR gene contribute to CBAVD (er) BMC Med. Genet. 8, 22 (2007)  
PUBMED 17448246  
REMARK GeneRIF: Identification of large rearrangements further expands the CFTR mutational spectrum in CBAVD  
REFERENCE 6 (bases 1 to 6132)  
AUTHORS Lissens,W., Bonduelle,M., Malfroot,A., Dab,I. and Liebaers,I.  
TITLE A serine to proline substitution (S1255P) in the second nucleotide binding fold of the cystic fibrosis gene  
JOURNAL Hum. Mol. Genet. 1 (6), 441-442 (1992)  
PUBMED 1284530  
REFERENCE 7 (bases 1 to 6132)  
AUTHORS Shackleton,S., Beards,F. and Harris,A.  
TITLE Detection of novel and rare mutations in exon 4 of the cystic fibrosis gene by SSCP  
JOURNAL Hum. Mol. Genet. 1 (6), 439-440 (1992)  
PUBMED 1284529  
REFERENCE 8 (bases 1 to 6132)  
AUTHORS Cheadle,J.P., Meredith,A.L. and al-Jader,L.N.  
TITLE A new missense mutation (R1283M) in exon 20 of the cystic fibrosis transmembrane conductance regulator gene  
JOURNAL Hum. Mol. Genet. 1 (2), 123-125 (1992)  
PUBMED 1284468  
REFERENCE 9 (bases 1 to 6132)  
AUTHORS Jones,C.T., McIntosh,I., Keston,M., Ferguson,A. and Brock,D.J.  
TITLE Three novel mutations in the cystic fibrosis gene detected by chemical cleavage: analysis of variant splicing and a nonsense mutation  
JOURNAL Hum. Mol. Genet. 1 (1), 11-17 (1992)  
PUBMED 1284466  
REFERENCE 10 (bases 1 to 6132)  
AUTHORS Tsui,L.C.  
TITLE Mutations and sequence variations detected in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: a report from the Cystic Fibrosis Genetic Analysis Consortium  
JOURNAL Hum. Mutat. 1 (3), 197-203 (1992)

PUBMED

1284534

REMARK

Review article

COMMENT

REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from [M28668.1](#), [AC000111.1](#) and [AC000061.1](#).  
On Mar 24, 2006 this sequence version replaced [gi:6995995](#).

Summary: This gene encodes a member of the ATP-binding cassette (ABC) transporter superfamily. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABCI, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MRP subfamily that is involved in multi-drug resistance. The encoded protein functions as a chloride channel and controls the regulation of other transport pathways. Mutations in this gene are associated with the autosomal recessive disorders cystic fibrosis and congenital bilateral aplasia of the vas deferens. Alternatively spliced transcript variants have been described, many of which result from mutations in this gene.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.  
COMPLETENESS: full length.

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	1973-1990	AC000111.1	131715-131732	
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	2629-2650	AC000111.1	134643-134664	
	2651-5731	M28668.1	2651-5731	
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FEATURES

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Location/Qualifiers

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5701 tgaattacat ttgtataaaa taatttttat atttgaaata ttgacttttt atggcactag
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6001 ccaccagtct gactgtttcc atcaagggtg cactgccttc tcaactcaa actgactctt  
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6121 atttgtgtga aa  
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## APPENDIX A.5

NCBI  Protein

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Books

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Display  Show  Send to

Range: from  to  Features: ☐ SNP ☒ CDD

☐ 1: [NP\\_000483](#). Reports cystic fibrosis t...[gi:90421313]

[BLink](#), [Conserved Domains](#), [Links](#)

[Comment](#) [Features](#) [Sequence](#)

LOCUS NP\_000483 1480 aa linear PRI 26-JUN-2007  
DEFINITION cystic fibrosis transmembrane conductance regulator [Homo sapiens].  
ACCESSION NP\_000483  
VERSION NP\_000483.3 GI:90421313  
DBSOURCE REFSEQ: accession [NM\\_000492.3](#)  
KEYWORDS .  
SOURCE Homo sapiens (human)  
ORGANISM Homo sapiens  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.  
REFERENCE 1 (residues 1 to 1480)  
AUTHORS Aznarez,I., Zielenski,J., Rommens,J.M., Blencowe,B.J. and Tsui,L.C.  
TITLE Exon skipping through the creation of a putative exonic splicing silencer as a consequence of the cystic fibrosis mutation R553X  
JOURNAL J. Med. Genet. 44 (5), 341-346 (2007)  
PUBMED 17475917  
REMARK GeneRIF: The effect of the R553X mutation on the splicing of exon 11 of the cystic fibrosis transmembrane conductance regulator gene was investigated.  
REFERENCE 2 (residues 1 to 1480)  
AUTHORS Preumont,V., Hermans,M.P., Lebecque,P. and Buysschaert,M.  
TITLE Glucose homeostasis and genotype-phenotype interplay in cystic fibrosis patients with CFTR gene deltaF508 mutation  
JOURNAL Diabetes Care 30 (5), 1187-1192 (2007)  
PUBMED 17337503  
REMARK GeneRIF: Insulin supplementation in diabetic subjects with CFTR deltaF508 mutation is a rational therapy for consideration, although this does not preclude that therapy directed toward insulin resistance may be involved.  
REFERENCE 3 (residues 1 to 1480)  
AUTHORS Bompadre,S.G., Sohma,Y., Li,M. and Hwang,T.C.  
TITLE G551D and G1349D, two CF-associated mutations in the signature sequences of CFTR, exhibit distinct gating defects  
JOURNAL J. Gen. Physiol. 129 (4), 285-298 (2007)  
PUBMED 17353351  
REMARK GeneRIF: CFTR's two ATP-binding pockets play distinct functional roles in gating  
REFERENCE 4 (residues 1 to 1480)  
AUTHORS Alonso,M.J., Heine-Suner,D., Calvo,M., Rosell,J., Gimenez,J., Ramos,M.D., Telleria,J.J., Palacio,A., Estivill,X. and Casals,T.  
TITLE Spectrum of mutations in the CFTR gene in cystic fibrosis patients of Spanish ancestry  
JOURNAL Ann. Hum. Genet. 71 (PT 2), 194-201 (2007)  
PUBMED 17331079  
REMARK GeneRIF: 121 disease-causing mutations were identified, accounting for 96% (1,877 out of 1,954) of CF alleles. Specific geographic distributions for the most common mutations, p.F508del, p.G542X, c.1811 + 1.6kbA > G and c.1609delCA, were confirmed.  
REFERENCE 5 (residues 1 to 1480)  
AUTHORS Taulan,M., Girardet,A., Guittard,C., Altieri,J.P., Templin,C., Beroud,C., des Georges,M. and Claustres,M.  
TITLE Large genomic rearrangements in the CFTR gene contribute to CBAVD (er) BMC Med. Genet. 8, 22 (2007)  
JOURNAL BMC Med. Genet. 8, 22 (2007)  
PUBMED 17448246  
REMARK GeneRIF: Identification of large rearrangements further expands the CFTR mutational spectrum in CBAVD  
REFERENCE 6 (residues 1 to 1480)  
AUTHORS Lissens,W., Bonduelle,M., Malfroot,A., Dab,I. and Liebaers,I.  
TITLE A serine to proline substitution (S1255P) in the second nucleotide binding fold of the cystic fibrosis gene  
JOURNAL Hum. Mol. Genet. 1 (6), 441-442 (1992)  
PUBMED 1284530  
REFERENCE 7 (residues 1 to 1480)  
AUTHORS Shackleton,S., Beards,F. and Harris,A.  
TITLE Detection of novel and rare mutations in exon 4 of the cystic fibrosis gene by SSCP  
JOURNAL Hum. Mol. Genet. 1 (6), 439-440 (1992)  
PUBMED 1284529  
REFERENCE 8 (residues 1 to 1480)  
AUTHORS Cheadle,J.P., Meredith,A.L. and al-Jader,L.N.  
TITLE A new missense mutation (R1283M) in exon 20 of the cystic fibrosis transmembrane conductance regulator gene  
JOURNAL Hum. Mol. Genet. 1 (2), 123-125 (1992)  
PUBMED 1284468  
REFERENCE 9 (residues 1 to 1480)  
AUTHORS Jones,C.T., McIntosh,I., Keston,M., Ferguson,A. and Brock,D.J.  
TITLE Three novel mutations in the cystic fibrosis gene detected by chemical cleavage: analysis of variant splicing and a nonsense mutation  
JOURNAL Hum. Mol. Genet. 1 (1), 11-17 (1992)  
PUBMED 1284466  
REFERENCE 10 (residues 1 to 1480)  
AUTHORS Tsui,L.C.  
TITLE Mutations and sequence variations detected in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: a report from the

JOURNAL Cystic Fibrosis Genetic Analysis Consortium  
 PUBMED Hum. Mutat. 1 (3), 197-203 (1992)  
 1284534  
 REMARK Review article  
 COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The  
 reference sequence was derived from [M28668.1](#), [AC000111.1](#) and  
[AC000061.1](#).  
 On Mar 24, 2006 this sequence version replaced [gi:6995996](#).

Summary: This gene encodes a member of the ATP-binding cassette (ABC) transporter superfamily. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABCI, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the MRP subfamily that is involved in multi-drug resistance. The encoded protein functions as a chloride channel and controls the regulation of other transport pathways. Mutations in this gene are associated with the autosomal recessive disorders cystic fibrosis and congenital bilateral aplasia of the vas deferens. Alternatively spliced transcript variants have been described, many of which result from mutations in this gene.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.

FEATURES

Location/Qualifiers

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 /db\_xref="taxon:9606"  
 /chromosome="7"  
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Protein 1..1480  
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 /note="ATP-binding cassette sub-family C, member 7"  
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 /db\_xref="CDD:31327"

Region 81..304  
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 /db\_xref="CDD:73050"

Region 443..625  
 /region\_name="ABC\_sbCCD"  
 /note="SbCCD and other Mre11/Rad50 (MR) complexes are implicated in the metabolism of DNA ends. They cleave ends sealed by hairpin structures and are thought to play a role in removing protein bound to DNA termini; cd03279"  
 /db\_xref="CDD:73038"

Region 850..1439  
 /region\_name="MdlB"  
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 /db\_xref="CDD:73048"

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## ORIGIN

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1441 ispsdrvklf phrnsskcks kpqiaalkee teeevqdtrl

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APPENDIX A.6

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- HomoloGene
- Map Viewer
- OMIM
- Probe
- RefSeq
- UniGene
- UniSTS

Resources

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- Tutorial

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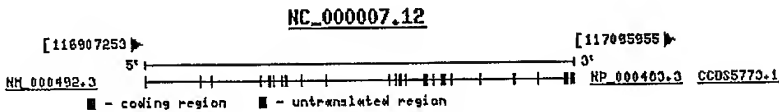
NCBI

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1: CFTR cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) [*Homo sapiens*]  
GeneID: 1080  
RefSeq status: Reviewed  
total gene size: 188703 bp  
updated 28-Jul-2007

Genomic regions, transcripts, and products

Go to reference sequence details



mRNA bp exons Protein aa exons  
NM\_000492.3 6132 27 NP\_000483.3 1480 27

**Exon information:**  
NM\_000492.3 length: 6132 bp, number of exons: 27  
NP\_000483.3 length: 1480 aa, number of exons: 27

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24291 - 24401	111 bp	24291 - 24401	111 bp	24402 - 29071	4670 bp
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50937 - 51152	216 bp	50937 - 51152	216 bp	51153 - 54313	3161 bp
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60138 - 60384	247 bp	60138 - 60384	247 bp	60385 - 62053	1669 bp
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186946 - 188703	1758 bp	186946 - 187146	201 bp		

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There are no related proceedings.